THE INTERNATIONAL LIVER CONGRESS™

Magnetic resonance elastography (MRE) demonstrate the strongest correlation with digital pathology and NASH CRN fibrosis assessments, compared to transient elastography and other assessed non-invasive tests (NITs)

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1 Introduction

Correlation of a non-invasive test (NIT) with liver histology-based readouts is one of the key aspects of NIT inclusion in clinical trials and their adoption and impact on patient care.

2 Aim

This sub-study aimed to explore correlation of different NITs with liver histology endpoints assessed by standard histology (NASH-CRN) and quantitative digital pathology (HistoIndex, HI-QDP).

3 Method

As part of the TANDEM NASH Phase 2 trial [NCT 03517540], the cross-sectional pre-treatment data has been collected from 269 patients with NAFLD (138 screen-failed and 131 randomized subjects). Key trial inclusion criteria were based on liver biopsy (NASH with F2 or F3 fibrosis).[1] Only subjects who signed additional research ICF have been included in this analysis. Liver biopsies were evaluated by a central reader using NASH-CRN scoring system and analyzed by HI-QDP algorithm. ALT, AST, ELF, GGT, FIB-4 and Pro-C3 were analyzed by central laboratory, Fibroscan liver stiffness measurement (LSM) was assessed by a clinical site, while MRE LSM was assessed by a central imaging reader.
In addition, SHG/TPEF microscopy was also used to assess liver fibrosis on a continuous scale (qFibrosis), as previously reported.[2]

4 Results

Statistical analysis on the entire cohort (n=269) revealed that MRE had the strongest correlation with both fibrosis assessments (NASH CRN and HI-QDP qFibrosis), followed by MRI aspartate aminotransferase (MAST) score (Table 1). As MRI and MRE imaging were only performed in a random subset of subjects, the MRE based dataset is smaller than for Fibroscan and soluble biomarkers. Interestingly, when correlating with qFibrosis, third and fourth ranked biomarkers were Pro-C3 and ELF, compared to FIB-4 and ELF when correlating with NASH CRN fibrosis assessment. In both cases, Fibroscan LSM and FibroScan-AST (FAST) score ranked fifth and sixth.

Correlation between histology readouts and NITs / R value (p value)		
NITs	**qFibrosis continuous**	**CRN**
ALT (qFibrosis n=266) (CRN n=254)	0.07 (p=0.2288)	0.02 (p=0.7472)
AST (qFibrosis n=266) (CRN n=254)	0.26 (p< 0.001)	0.25 (p< 0.001)
ELF (qFibrosis n=266) (CRN n=255)	0.33 (p< 0.001)	0.38 (p< 0.001)
GGT (qFibrosis n=267) (CRN n=255)	0.22 (p< 0.001)	0.18 (p=0.0040)
PRO-C3 (qFibrosis n=102) (CRN n=102)	0.35 (p< 0.001)	0.08 (p=0.4442)
FIB-4 (qFibrosis n=262) (CRN n=251)	0.26 (p< 0.001)	0.40 (p< 0.001)
Fibroscan LSM (kPa) (qFibrosis n=183) (CRN n=181)	0.29 (p< 0.001)	0.21 (p=0.0039)
FAST (qFibrosis n=151) (CRN n=149)	0.26 (p=0.0011)	0.28 (p< 0.001)
MRE LSM (kPa) (qFibrosis n=32) (CRN n=31)	0.49 (p=0.0047)	0.49 (p=0.0053)
MAST (qFibrosis n=32) (CRN n=31)	0.38 (p=0.0324)	0.43 (p=0.0149)

Table 1: Correlation between CRN staging and qFibrosis continuous values against NITs. R value is calculated using Spearman correlation.
Abbreviations: **NITs**: non-invasive tests; **n**: number of patients in individual group; **ALT**: Alanine Aminotransferease; **AST**: Aspartate transaminase; **ELF**: Enhanced liver fibrosis test; **GGT**: Gamma-glutamyl transferase test; **PRO-C3**: precisely cleaved N-terminal propeptide of type III collagen; **FIB-4**: Fibrosis-4 index; **LSM**: liver stiffness measurement; **FAST**: FibroScan-AST score; **MRE**: Magnetic resonance elastography; **MAST**: MRI-based score

5 Conclusions

Imaging based endpoints, MRE LSM and MAST score, had the strongest correlation with liver fibrosis staging (both NASH CRN and by HI-QDP qFibrosis) among tested NITs.

6 Acknowledgements

The authors thank the patients who participated in this study and their families, as well as the investigators and the study coordinators.

7 References

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Imaging based endpoints, MRE LSM and MAST score, had the strongest correlation with liver fibrosis staging (both NASH CRN and HistoIndex-QDP qFibrosis)

Individual, blood-based non-invasive tests show only weak to moderate correlation with the degree of fibrosis in liver biopsy

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